REMARKS

Claims 1-52 are pending in the application. Claims 13-15 have been examined. Claims 1-12 and 16-52 have been withdrawn by the Office due to a Restriction Requirement.

The Specification has been amended, as suggested by the Office Action, to indicate that the present application "claims benefit of International Application No. PCT/US04/30530 filed September 20, 2004, which claim benefit of priority from U.S. Provisional Application No. 60/504,044, filed September 19, 2003."

The Specification has been amended at page 6, line 22 to page 7, line 8 in the "BRIEF DESCRIPTION OF THE DARWINGS" to include reference to the SEQ ID NO.'s depicted in Figure 1a for MEPE in man (SEQ ID NO. 25), in the mouse (SEQ ID NO. 26), and in the rat (SEQ ID NO. 27).

The Specification has been further amended at page 9, line 21 to page 10, line 22 in the "BRIEF DESCRIPTION OF THE DARWINGS" to include reference to the SEQ ID NO.'s depicted in Figure 8a for human-DMP-1(SEQ ID NO. 28), human-MEPE(SEQ ID NO. 29), mouse-MEPE (SEQ ID NO. 30), rat-MEPE (SEQ ID NO. 31), and human-Statherin (SEQ ID NO. 32).

The Specification has been further amended at page 16, lines 25-27 in the "BRIEF DESCRIPTION OF THE DARWINGS" to include reference to the SEQ ID NO.'s depicted in Figure 43 for macaque monkey (SEQ ID NO. 33), murine (SEQ ID NO. 34), rat (SEQ ID NO. 35), MEPE (SEQ ID NO. 36), and consensus (SEQ ID NO. 37).

The original sequence listing has been replaced with a new sequence listing which now includes new SEQ ID NO.'s 25- 37.

Claim 13 has been amended to recite that ASARM is defined as "acidic-serine-rich-MEPE" in its first appearance. By this amendment no new matter has been added.

Further, withdrawn Claims 1, 5, 10, 11, 24, 32, 40, 47, 49, and 50 have also been amended to recite the definition of ASARM in its first appearance.

By these amendments no new matter has been added.

OBJECTION TO THE SPECIFICATION - COMPLIANCE WITH SEQUENCE RULES

The Office Action has objected to the specification under 37 C.F.R. §§1.821(a)(1) and (a)(2) alleging that Figures 1a, 8a, and 43 contain amino acid sequences that are not described using a SEQ ID NO. Applicants believe the amendments to the specification obviate this object.

OBJECTION TO THE CLAIMS

The Office Action has objected to Claims 13-15 because of the use of the abbreviation ASARM should be spelled out on a first appearance in the claims. The amendment to Claim 13 obviates the objection.

REJECTION UNDER 35 U.S.C. § 112

The Office Action has rejected Claims 13-15 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicant respectfully traversed this rejection.

The Office Action states "[t]he instant specification teaches a method comprising administering ASARM peptide of SEQ ID NO. 1-5, 8, 9, 13, 14, and 16 for treating or inhibiting ectopic tissue mineralization in a subject. However, the breadth of [the claims] includes a method comprising administering a very widely varying genus ASARM peptide because the "ASARM peptide disclosed herein can also comprise any ASARM peptide or variant thereof," which encompasses a method of administering any polypeptide given broad and reasonable interpretation of "fragment" or "variant of ASARM peptide." The Office Action further states the "prior art and the instant specification do not describe [a] method of administering any ASARM peptide as described by the breadth of [the] claim above for inhibiting ectopic mineralization in a subject."

Figure 1a depicts the acidic-serine-aspartate-rich-MEPE peptide motif for human, mouse, and rat species. As depicted in Figure 1a, the carboxy terminal residues of ASARM are highly conserved from species to species. The release of this fragment from any of these species would provide a peptide motif that is resistant to proteases, and as such, provide a method for controlling ectopic mineralization.

The ASARM-peptide is enriched in aspartic acid, serine, and glutamic acid. When activated, the serine residues are diversely phosphorylated and the peptide has a low pI, is acidic, hydrophilic and has a relatively low molecular weight (2-4 kDA). Structurally, the disposition of the aspartic acid, serine, and glutamic acid residues is such that the aspartic acid residues occur at the N-terminus in doublets or triples followed by singlets, doublets or triplets of serine residues followed by glutamic acid or glycine residues. This unique combination of amino acids is only found in "ASARM peptide or variant thereof."

As indicated in Figure 1b, the ASARM-motif is found in the mid-region of osteopontin rather that in the terminal region of MEPE. VandenBos (VandenBos, A.L.J.J. *et al.* "Blood Circulation as Source for Osteopontin in Acelluar Extrinsic Fiber Cementum and Other Mineralizing Tissues," *J. Dent. Res.* **78**(11): 1685-1695, (1999)) disclose that osteopontin is effective in mineralizing tissues, not only when derived from a local cellular source, but may also be imported from outside the local environment. Although VandenBos does not describe the ASARM peptide sequence, Applicant clearly points out the presence of this motif in osteopontin (see, Figure 1b). Moreover, when the teaching of VandenBos are taken together with Applicant's disclosure in Figure 1a that the sequence of ASARM is highly conserved from species to species, these facts demonstrate that the peptide sequences of ASARM-motifs are highly conserved and, as such, "ASARM peptide or variant thereof " as recited in Claim 13 would be expected to affect ectopic tissue mineralization.

The Office Action has also rejected Claims 13-15 under 35 U.S.C. § 112, first paragraph, while being enabling for a method comprising administering the ASARM peptide of SEQ ID NO. 1-5, 8, 9, 13, 14, and 16, is allegedly not enabled for administering any ASARM peptide as described the breadth of claims. Applicant respectfully disagrees.

Claim 13 as amended recites "administering acidic-serine-rich-MEPE (ASARM) peptide to [a] subject." The figures, examples, and specification point out the unique combination of amino acids, inter alia, serine, glutamic and aspartic acids, that comprise ASARM peptide and how these amino acids are highly conserved from species to species (Figure 1a) and from peptide to peptide (Figure 1b).

Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 102(b)

The Office Action has rejected Claims 13-15 under 35 U.S.C. § 102(b), as allegedly anticipated by VandenBos, A.L.J.J. *et al.* "Blood Circulation as Source for Osteopontin in Acelluar Extrinsic Fiber Cementum and Other Mineralizing Tissues," *J. Dent. Res.* **78**(11): 1685-1695, (1999) (hereinafter "VandenBos") as evidenced by McKee *et al.*, *Microsc. Res.. Tech.*, Vol. 33, pp 141-164 (1996) (herein after "McKee"). The Office Action's rejection is respectfully traversed.

The Office Action states "[a]ccording to MPEP §2111.02, II, "During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. It is noted that the recitation of "treating or inhibiting ectopic tissue mineralization in the subject" before the term "comprising" in Claim 13 is a preamble reciting intended use and do not contribute to a manipulative difference in recited steps of administering ASARM peptide."

VandenBos does not teach that osteopontin inhibits mineralization. VandenBos teaches that osteopontin is associated with **mineralizing and not de-mineralizing tissue** as taught by Applicant. Moreover, VandenBos undertakes an investigation using the calcium chelator EDTA to determine the amount of mineralization that takes place in bone *in vivo*. The Office Action states "VandenBos et al. teach ...[that] osteopontin functions "as an **inhibitor** of mineralization." (Emphasis added.) VandenBos does not teach that osteopontin is a mineralization inhibitor, instead VandenBos teaches at page 1690, column 2, line 7 of the paragraph titled "Mineralizing collagen sheets "[a]s the carrier material mineralized, a progressive influx of ^{125}I-OPN was observed." Moreover, in the same section at paragraph 3, VandenBos teacher "[w]hile all control implants proved to be OPN-negative, alkalie-phosphatse-complexed implants stained positive with the OPN antibody. **The immunostaining was restricted to the mineralized areas**." (Emphasis added.)

VandenBos relates to mineralization of bone by osteopontin. VandenBos does not mention ASARM. The presence of an ASARM-like motif in osteopontin, DMP1 does not indicate that the motif in these larger protein molecules inhibits mineralization, instead, the reverse is the case and in an intact protein such as DMP-1, the ASARM-motif acts as a nucleator

of mineralization sequestration and serves to epistatically orient hydroxyapatite during formation.

The Office Action has misconstrued the disclosure of VandenBos. VandenBos does not teach the subject matter of the present application as recited in Claim 13. Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 25-32 under 35 U.S.C. § 103(a).

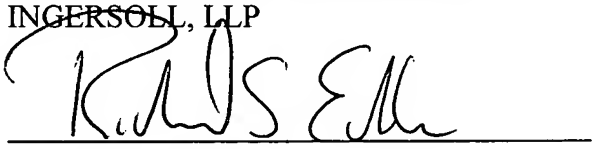
CONCLUSION

The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $525.00 under 37 C.F.R. § 1.17(a)(3) for a Three-Month Extension of Time (small entity) is enclosed herewith. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

BALLARD SPAHR ANDREWS & INGERSOLL, LLP



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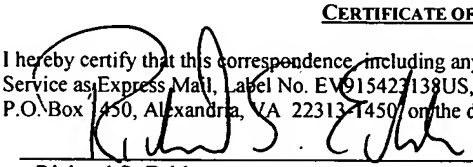

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